ANNEX

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE ADDRESSED TO THE MEMBER STATES

The EU Member States shall ensure that:

The MAH sets up a surveillance programme to collect information on: the demographics of patients prescribed Thelin, any adverse reactions and reasons for discontinuation of Thelin and that this surveillance programme is put in place prior to marketing of the product.

The MAH agrees the details of a controlled distribution system with the National Competent Authority and implements such a programme nationally to ensure that, prior to prescribing, all doctors who intend to prescribe Thelin are provided with a physician information pack containing the following:

- Product information
- Physician information about Thelin
- Patient information card
- Partner of patient information card

The physician information about Thelin should contain the following key elements:

- That Thelin is teratogenic
    - Need for pregnancy testing prior to first and subsequent prescriptions
    - Use of effective contraception in women of child bearing age
    - Possible interaction with oral contraceptives and increased risk of thromboembolism
    - Need to advise female patients about teratogenicity, need for pregnancy testing and contraception, what to do if they become pregnant
    - Referral of patients who become pregnant to a physician specialised or experienced in teratology and its diagnosis for evaluation and advice

- That Thelin is hepatotoxic
    - Need for liver function tests prior to and during treatment
    - Contraindication in patients with pre-existing hepatic disease
    - Discontinue sitaxentan sodium immediately if liver enzymes rise above 5 x ULN
    - Need for close monitoring if liver enzymes measure between 3 and 5 x ULN, with discontinuation if a repeat analysis is above 3 x ULN, and not restarted until levels have returned to below 3 x ULN

- That treatment with Thelin often causes a decrease in haemoglobin and related red cell parameters
    - Need for full blood count prior to use and monitoring at clinically appropriate intervals

- That there is an increased risk of bleeding with Thelin
    - Interaction with warfarin and vitamin K antagonists leading to an increased INR
    - Need to decrease established dose of vitamin K antagonist upon starting sitaxentan therapy
    - Start vitamin K antagonists treatment at a reduced dose if already on sitaxentan sodium
    - Need for regular monitoring of INR
    - Co-prescription with sildenafil may increase the risk of haemorrhage
    - Be aware of the potential for haemorrhage and investigate as appropriate

- That there is an interaction with cyclosporin A which may lead to higher blood concentration of Thelin and hence an increased risk of adverse reactions.

- That the safety database of Thelin is limited and physicians are encouraged to enrol patients in a surveillance programme to increase knowledge about the incidence of important adverse drug reactions (ADRs). The surveillance programme should prompt doctors to report serious ADRs and certain selected ADRs as below immediately and other non-serious ADRs at three monthly intervals.
  The information collected should include:
  - Anonymised patient details – age, sex and aetiology of PAH
  - Concomitant medications
  - Reason for discontinuation
  - ADRs
    - All serious ADRs
    - Increase in hepatic enzymes to > 3 x ULN
    - Anaemia
    - Haemorrhage
    - Pregnancy and outcome
    - Pulmonary oedema
    - Suspected interactions
    - Unexpected ADRs according to the SPC.

The Patient information card should include the following information

- That Thelin is teratogenic
- The need for a negative pregnancy test immediately prior to first prescription
- The need to ensure that women of child bearing age are using effective contraception and that patients should inform their doctors of any possibility of pregnancy before a new prescription is issued
- The need for female patients to contact their treating doctor immediately if they suspect that they might be pregnant.
- That Thelin is hepatotoxic and they will need to attend for regular blood tests
- That Thelin may cause bleeding
- The need to tell their doctor about any adverse events
- The need to tell health care practitioners that they are taking Thelin

Partner of patient information card should include the following information:

- That Thelin is teratogenic and that women of child bearing age must use effective contraception